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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,460	01/17/2006	David Alland	UMD-0112	4649

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/540,460	ALLAND ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 4, 2009 has been entered.

2. Applicant's amendments to the claims and remarks presented in the reply of February 4, 2009 have been fully considered but are not persuasive to place all claims in condition for allowance.

All rejections not reiterated herein are hereby withdrawn.

In particular, the objection to the amendment filed June 5, 2008 has been obviated by the amendment to the specification.

The rejection of claims 1-7 under 35 U.S.C. 112, second paragraph and the rejection of claims 1-7 under 35 U.S.C. 112, first paragraph (new matter) have been obviated by the amendment to the claims.

3. Claims 1-7 are pending and have been examined herein.

Maintained Rejections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. It is noted that the following rejections were previously presented in the Office action of September 4, 2008 and have been modified herein to address the amendments to the claims.

6. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (U.S. Patent No. 6,090,552, 7/18/2000) as evidenced by GenBank Accession No. NM_000025 (April 1999), in view of Matsuzaki (U.S. Patent No. 6,333,179; cited in the IDS of June 22, 2005), Metallinos (U.S. Patent No. 6,372,900, cited in the IDS of June 22, 2005), and Lopez (U.S. Patent No. 6,514,698).

Nazarenko (see column 27; and col. 56-57, Example 10) teaches a method for detecting the presence of a single nucleotide polymorphism or a mutation in a target nucleic acid in an organism wherein the method comprises: (i) amplifying a nucleic acid sequence using a hairpin primer, wherein the hairpin primer terminates at a polymorphic

position, such that the 3' nucleotide of the hairpin primer is located at the position of the single nucleotide polymorphism or mutation; and (ii) measuring the amount of amplification product wherein a decrease in the amplification product is indicative of the presence of a polymorphism or mutation (i.e., a mismatch between the hairpin primer and the target nucleic acid). Nazarenko (column 27) teaches that in the method of allele-specific PCR, "(u)nder the appropriate reaction conditions, the target DNA is not amplified if there is a base mismatch."

At col. 56, Nazarenko exemplifies the method of using the allele-specific hairpin primers in an Amplification Refractory Mutation System (ARMS) Assay. Since Nazarenko teaches using the allele-specific hairpin primers in the ARMS assay, the method of Nazarenko is considered to be a modified ARMS assay. In the modified ARMS assay (col. 56-57), the amount of amplification product obtained using a hairpin primer that is fully complementary to the target sequence is compared to the amount of amplification product obtained using a hairpin primer that includes a mismatch with the target sequence, and a decrease in the amount of amplification product indicates a mismatch between the hairpin primer and the target nucleic acid, and thereby indicates the presence of a single nucleotide polymorphism in the organism.

Regarding the recitation in the claims that the method is one which amplifies a 30 to 90 base pair nucleic acid molecule of an organism, the method exemplified by Nazarenko (col. 56-57) results in the amplification of 101 base pairs of the B3AR (i.e., adrenergic receptor beta-3 nucleic acid / ADRB3) nucleic acid. The fact that the method of Nazarenko results in the amplification of 101 bp of an organisms' ADRB3 nucleic acid

is evidenced by the teachings of GenBank Accession No. NM_000025 wherein the nucleotide positions to which the forward and reverse primers of Nazarenko (Table 5) hybridize are disclosed. Specifically, the forward hairpin primer of Nazarenko hybridizes to nucleotides 368-387 of B3AR nucleic acids, and the reverse primer of Nazarenko hybridizes to the inverse complement of nucleotides 449-468 of B3AR, thereby generating a product containing 101bp (and thus 30 to 90bp) of an organisms' B3AR nucleic acid.

Nazarenko does not teach a method wherein the amplification product is of a length of 30 to 90bp.

However, Matsuzaki teaches that methods of PCR are more efficient when shorter length nucleic acids are amplified. Matsuzaki (col. 1, lines 43-46) states that "The yield of longer amplicons is often less than the yield of shorter amplicons because those differences in PCR amplification efficiency." Matsuzaki (Table 3, and col. 4-5) exemplifies methods of producing amplicons of 90 bp. Lopez also teaches that methods that produce short PCR products of 30-100bp provide several advantages. It is stated that "Since the PCR reaction cycle times are shortened to a few seconds, the concentrations of the amplified DNA are increased, resulting in improved signal to noise ratio" (col. 4, lines 49-54). Lopez also states that "the use of short PCR products allows for faster amplification times and improved sensitivity through stronger signals due to higher molar concentrations" (col. 14, lines 9-12). Further, Metallinos (col. 11, lines 20-27) exemplifies methods of allele specific PCR in which the amplification products are of a length of 90 bp.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have selected PCR primers that produced amplicons of a shorter length, and particularly amplicons of a length of 30-90 bp, in order to have improved the efficiency of the PCR assay, thereby increasing the yield of the amplification product and the sensitivity of detection of a single nucleotide polymorphism or mutation.

Regarding claim 2, in the method of Nazarenko, the nucleic acid is amplified by PCR (col. 53).

Regarding claim 3, Nazarenko exemplifies methods wherein the hairpin primer comprise DNA (Table 5), but does not exemplify methods wherein the hairpin primer comprises RNA. However, Nazarenko (col. 17, lines 36-40) does teach that the hairpin primer may be DNA or RNA. Accordingly, the use of a hairpin primer comprising RNA in the method of Nazarenko would have been obvious to one of ordinary skill in the art at the time the invention was made because this would have provided an equally effective means to produce an amplification product of 30 to 90bp, and thereby an equally effective means for detecting a single nucleotide polymorphism in an organism.

Regarding claim 4, Nazarenko teaches detecting PCR amplification products at the completion of the PCR assay (col. 53-54).

Regarding claim 5, the hairpin primers exemplified by Nazarenko comprise DNA (Table 5).

Regarding claim 6, Nazarenko (col. 53-54) exemplifies methods using allele-specific hairpin primers wherein the PCR amplification products are detected at the

completion of the PCR assay, but does not exemplify methods using allele-specific hairpin primers wherein the PCR amplification products are detected using real-time PCR. However, Nazarenko does teach that in methods in which the amplification product is formed using a hairpin primer, the amplification product can be detected by real-time PCR (see col. 43 and 48). It is stated that real-time PCR detection provides the advantages of allowing researches to perform the method in closed tubes, thereby eliminating the risk of carry-over contamination, simplifies the detection assay, and permits quantification of the amplification products over a wide dynamic range. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have detected the amplification products using real-time PCR in order to have provided an effective means for monitoring the allele-specific amplification reaction which would simply the detection method, reduce cross-contamination and allow for a highly accurate quantification of the amplification products.

7. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko, as evidenced by GenBank Accession No. NM_000025 (April 1999), in view of Matsuzaki, Metallinos, and Lopez, and further in view of Tyagi (U.S. Patent No. 6,365,729; cited in the IDS).

The teachings of Nazarenko, Matsuzaki, Metallinos and Lopez are presented above.

Nazarenko exemplifies methods wherein the hairpin primer comprises DNA (Table 5) and teaches that the hairpin primer may also comprise RNA or may be

modified in the base, sugar or phosphate backbone (co. 17, lines 36 to col. 18, line 11). However, Nazarenko does not exemplify methods wherein the hairpin primer comprises a PNA.

Tyagi (col. 3 and 6) teaches a method of allele-specific PCR using hairpin primers. Tyagi (column 2) teaches that "if the binding of the primer in the tube to the target sequence creates a mismatched 3'-terminal nucleotide, then the primer cannot be efficiently extended by incubation with DNA polymerase. Amplification of the mismatched template is significantly delayed." Tyagi (column 6) further teaches that hairpin primers used for allele-specific PCR may contain PNAs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have performed the allele-specific PCR method using hairpin primers that contain PNAs in view of the well known benefits provided by PNAs of enhancing the stability of hybridization and improving the ability to distinguish between perfectly matched and mismatched sequences. Thereby, one would have been motivated to have used PNA hairpin primers in order to have provided a highly sensitive and effective method for detecting the presence of a polymorphism or mutation.

Response to Remarks

8. In the reply of February 4, 2009, Applicants traversed the previous grounds of rejection.

Applicants state that Examples 5 and 6 describe experiments wherein comparisons of the original ARMS assay with the modified ARMS assay showed

superiority of the modified ARMS assay of the instant application. It is stated that the original ARMS assay identified the SNP in only 7 of 13 assays, whiled the modified ARMS assay of the instant invention identified the correct SNP in all 13 assays. Applicants point to Table 2 and page 17 in support of these arguments.

Applicants arguments and the cited teachings in the specification have been fully considered but are not persuasive. The teachings in the specification establish the improved results obtained when using the hairpin primer in the ARMS assay as compared to when using a linear primer in the ARMS assay. However, the cited primary reference of Nazarenko teaches performing the ARMS assay using hairpin primers. Accordingly, Applicants have not established any improved results over the method of Nazarenko since both the method of the present invention and the method of Nazarenko are modified ARMS assays that use a hairpin primer. Note that "(e)vidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims" (MPEP 706.02; emphasis added). It is noted that MPEP 706.02(e) teaches that Applicant may compare the claimed invention with prior art that is different than that applied by the examiner, but that the prior art relied upon must still be the most closely related prior art. However, in the present situation, the asserted unexpected properties are not relative to the closest prior art - i.e., the prior art of Nazarenko teaching the modified ARMS assay using hairpin primers.

The response states that the combinations of cited references do not teach or suggest the modified ARMS assay of the present invention. Applicants cite KSR s

stating that when considering the obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." Applicants conclude that the superior properties of the instant claimed invention rebuts any prima facie case of obviousness.

These arguments have also been fully considered but are not persuasive. Again, the superior results asserted by Applicant are not with respect to the closest prior art applied (the modified ARMS assay of Nazarenko which relies on the use of hairpin primers), but with respect to the prior art in general (the "original" ARMS assay using linear primers). Accordingly, Applicants have not in fact established any improved results with respect to the applied prior art. Further, the method of Nazarenko differs from the claimed invention only with respect to the fact that Nazarenko exemplifies a method wherein the amplification product is 101bp in length, whereas the present invention exemplifies methods wherein the amplification product is 30-90bp in length. However, the cited prior art of Matsuzaki and Lopez each teach the advantages of performing PCR using primers that generate amplicons of a smaller length, including amplicons of 30-90 bp. In particular, Matsuzaki teaches that methods of PCR are more efficient when shorter length nucleic acids are amplified, and specifically exemplifies methods of producing amplicons of 90 bp. Lopez also teaches that methods that produce short PCR products of 30-100bp provide several advantages, including the improvements of increasing the concentrations of the amplified DNA and improving the signal to noise ratio. Further, Metallinos (col. 11, lines 20-27) exemplifies methods of

allele specific PCR in which the amplification products are of a length of 90 bp. Thereby, the cited prior art teaches that PCR methods that produce amplicons of a shorter length, and particularly amplicons of a length of 30-90 bp, improve the efficiency of the PCR assay, thereby increasing the yield of the amplification product and the sensitivity of detection of a single nucleotide polymorphism or mutation. Accordingly, any improved results obtained in methods in which the amplicon is 30-90 bp would have been expected in view of the teachings of Matsuzaki, Lopez and Metallinos. Further, the results of the combination would have been predictable since Matsuzaki, Lopez and Metallinos teach selecting primers to yield amplicons of 30-90bp, and Metallinos particularly teaches using allele specific primers to yield amplicons of 90bp and because Matsuzaki and Lopez teach that performing PCR to produce products of 30-90bp provides improved results that increase the yield of amplification product and reduce background signal, thereby improving the sensitivity of PCR detection assays.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634